DETAILED ACTION

Status of Application

1. The remarks and amendments filed on 03/29/10 are acknowledged.

2. Claims 1-24 were cancelled.

3. New claims 25-44 were added and are included in the prosecution.

Response to Arguments

Rejection of claims under 35 USC § 103(a)

4. In light of the cancellation of claims 1-8, 10-13 and 20-24, the rejections with respect to these claims are rendered moot.

5. Applicant's arguments, see Page 5, filed 03/29/10, with respect to the patentability of the newly added claims over Ko et al. (Journal of Microencapsulation 1998) in view of Whittle et al. (US 2002/0136752 A1) and further in view of Bechgaard et al. (US 5,397,771) have been fully considered but are not persuasive. Applicant's arguments with respect to Ko, Whittle, Bechgaard and Patel et al. (US 6,248,363) have been fully considered but are not persuasive. Applicant's arguments with respect to Ko, Whittle, Bechgaard and Lacy et al. (US 5,645,856) have been fully considered but are not persuasive.

Applicant argues that none of the cited references refers to a lipophilic formulation wherein the at least one sexual hormone drug is maintained at a serum level greater than baseline for at least six hours after a single application of the formulation.

This is not persuasive because the claimed composition and its components (the sexual hormone drug, an oil and a surfactant) are known in the art for nasal administration, and testing the serum level of the active ingredient over time and modification of the composition to achieve desired serum levels is part of routine optimization unless there is evidence of criticality or unexpected results.

Therefore, the rejections are applied to new claims 25-44.

Additionally, rejections are made over Gizurarson et al. (US 2004/0005275 A1) and over Heckenmüller et al. (US 5,514,673).

Since these rejections were necessitated by Applicant's amendment, this action is made FINAL.

Claim Objections

6. Claim 31 is objected to because of the following informalities: line 3 of claim 31 has a typographical error; "polyoxyethylensorbitans" should be corrected to recite " polyoxyethylene sorbitans".

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 25-26, 28-31, 33-34 and 40-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ko et al. (Journal of Microencapsulation 1998).

The claimed invention is a lipophilic formulation for nasal application comprising: a) at least one sexual hormone drug; b) at least one lipophilic or partly lipophilic carrier comprising an oil; and c) a compound or a mixture of compounds having a surface tension decreasing activity, wherein the at least one sexual hormone drug is maintained at a serum level greater than baseline for at least six hours after a single application of the formulation.

Ko teaches emulsion formulations of testosterone for nasal delivery (Abstract). The formulation materials include vegetable oil and surfactants (Page 198, Materials). The formulations are prepared by emulsification of the oil phase (containing the lipophilic testosterone and soybean oil) with the aqueous phase (further containing a surfactant) (Page 199, Preparation of formulations).

Ko does not expressly teach that the at least one sexual hormone drug is maintained at a serum level greater than baseline for at least six hours after a single application of the formulation.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make an emulsion formulation comprising testosterone, soybean oil and surfactant, as taught by Ko, test the serum level of testosterone and modify the formulation in order to achieve a serum level of greater than baseline for at least six hours after a single application during the process of routine experimentation.

One of ordinary skill in the art would do this because the components of the claimed composition are known in the art and testing the serum level of the active ingredient over time and modification of the composition to achieve desired serum

levels is part of routine optimization unless there is evidence of criticality or unexpected results.

Regarding claim 25, components a, b and c of the lipophilic formulation would have been obvious over the emulsion formulations of testosterone for nasal delivery including vegetable oil and surfactants, as taught by Ko (Abstract and Page 198, Materials). The limitation of the at least one sexual hormone drug maintained at a serum level greater than baseline for at least six hours after a single application of the formulation would have been obvious over the testosterone formulation taught by Ko because testing the serum level of the active ingredient over time and modification of the composition to achieve desired serum levels is part of routine optimization unless there is evidence of criticality or unexpected results.

Regarding claim 26, the vegetable oil would have been obvious over the vegetable oil taught by Ko (Page 198, Materials).

Regarding claims 28-30, the oil in an amount between 30% and 98% would have been obvious over the calculated amount of vegetable oil (40g/42g total oil phase) 95.24%, as taught by Ko (Page 199, Preparation of formulations).

Regarding claim 31, component (c) would have been obvious over the $TWEEN_{80}$ (polyoxyethylene sorbitan monooleate) taught by Ko (Page 199, Preparation of formulations).

Regarding claims 33-34, component (c) in an amount between 1% and 20% would have been obvious over the calculated amount of $SPAN_{80}$ (1g/42g total oil phase) 2.38%, as taught by Ko (Page 199, Preparation of formulations).

Regarding claims 40-42, the sexual hormone drug in an amount between 0.5% and 6% would have been obvious over the calculated amount of testosterone (1g/42g total oil phase) 2.38%, as taught by Ko (Page 199, Preparation of formulations).

Regarding claim 43, the limitation of the at least one sexual hormone drug maintained at a serum level greater than baseline for at least ten hours after a single application of the formulation would have been obvious over the testosterone formulation taught by Ko because testing the serum level of the active ingredient over time and modification of the composition to achieve desired serum levels is part of routine optimization unless there is evidence of criticality or unexpected results.

9. Claims 27, 35-36, 38-39 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ko et al. (Journal of Microencapsulation 1998) in view of Whittle et al. (US 2002/0136752 A1) and further in view of Bechgaard et al. (US 5,397,771).

The teaching of Ko is stated above.

Ko does not expressly teach castor oil or a formulation free of water.

Whittle teaches a pharmaceutical formulation for use in the administration of a lipophilic medicament via a mucosal surface, the formulation comprising at least one lipophilic medicament and a matrix comprising at least one self emulsifying agent which when hydrated forms an emulsion containing the lipophilic medicament which is capable of adhering reversibly to a mucosal surface and allowing controlled release of the medicament (Page 1, [0001] and [0009]). Whittle teaches that "lipophilic medicaments can be effectively brought into intimidate contact with the absorptive mucous membrane

when they are formulated in a self-emulsifying matrix" (Page 1, [0010]). "The matrix may further comprise one or more viscolising agents (agents which increase viscosity)" (Page 1, [0011]). Self-emulsifying surfactants, viscolising agents with adhesive properties such as sugar alcohols are disclosed (Page 2, [0020]).

Bechgaard teaches that vehicles used for nasal administration of biologically active substances possess lipophilic properties (Col. 1, lines 40-48). The biologically active substances include testosterone (Col. 5, lines 39-40 and Col. 6, lines 43-44). The pharmaceutical preparation also comprises surfactants (Col. 7, lines 55-58). Hydrophobic (and lipophilic) agents including castor oil are disclosed (Col. 10, lines 64-66). An anhydrous vehicle used in the method of administering a biologically active substance is disclosed (Col. 34, claim 8, lines 39-40).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make an emulsion formulation comprising testosterone, soybean oil and surfactant, as taught by Ko, test the serum level of testosterone and modify the formulation in order to achieve a serum level of greater than baseline for at least six hours after a single application during the process of routine experimentation, combine it with the self-emulsifying formulation comprising a lipophilic medicament, as taught by Whittle, further combine it with the anhydrous composition for nasal delivery comprising oils and testosterone, as taught by Bechgaard, and produce the instant invention.

One of ordinary skill in the art would do this because preparing a composition suitable for nasal administration that is anhydrous and contains testosterone as the active agent, castor oil as the lipophilic agent and surfactants was known in the art, as

evidenced by Bechgaard. One of ordinary skill in the art would combine this known technique with the teachings of Ko and Whittle because Bechgaard teaches that an anhydrous formulation may be useful in chronic dosing (Col. 25, lines 67-68).

Regarding instant claim 27, the castor oil would have been obvious over the castor oil taught by Bechgaard (Col. 10, lines 64-66).

Regarding instant claim 35-36 and 38-39, the viscosity regulating agent would have been obvious over the viscolising agent (Page 1, [0011]) including beeswax (Page 4, [0050]), sugars and starches (Page 4, [0045], [0052]) taught by Whittle. The limitation of the viscosity regulating agent in an amount between 0.5% and 10% would have been obvious because one of ordinary skill in the art would use different levels of a viscosity regulating material in order to achieve the desired viscosity, unless there is evidence of criticality or unexpected results.

Regarding instant claim 44, the limitation of the formulation that is free of water would have been obvious over the self emulsifying formulation taught by Whittle (Page 1, [0001] and [0009]) in view of the anhydrous vehicle used in the method of administering a biologically active substance, as taught by Bechgaard (Col. 34, claim 8, lines 39-40).

10. Claim 32 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ko et al. (Journal of Microencapsulation 1998) in view of Whittle et al. (US 2002/0136752 A1) and further in view of Bechgaard et al. (US 5,397,771) and Patel et al. (US 6,248,363).

The teachings of Ko, Whittle and Bechgaard are stated above.

Ko, Whittle and Bechgaard do not expressly teach oleoyl macrogolglyceride as the surfactant.

Patel teaches that the bioavailability of drugs (Col. 6, line 49) can be improved by their invention, which includes macrogolglycerides as the surfactant (Col. 35, line 46, Col. 65, lines 50-53, claim 16).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make an emulsion formulation of testosterone, as taught by Ko, test the serum level of testosterone and modify the formulation in order to achieve a serum level of greater than baseline for at least six hours after a single application during the process of routine experimentation, combine it with the self-emulsifying formulation comprising a lipophilic medicament, as taught by Whittle, further combine it with the anhydrous composition for nasal delivery comprising oils and testosterone, as taught by Bechgaard, use the oleoyl macrogolglyceride taught by Patel, and produce the instant invention.

A person with ordinary skill in the art at the time the invention was made would have used a variety of macrogolglycerides for surfactants. These macrogolglycerides would include different fatty acid esters and oleoyl macrogolglyceride. The motivation to use these surfactants would be to allow the emulsification and improve the bioavailability of poorly soluble, lipophilic drugs

Regarding instant claim 32, the limitation of oleoyl macrogolglyceride would have been obvious over the oleoyl macrogolglyceride taught by Patel (Col. 35, line 46, Col. 65, lines 40-53, claim 16).

11. Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ko et al. (Journal of Microencapsulation 1998) in view of Whittle et al. (US 2002/0136752 A1) and further in view of Bechgaard et al. (US 5,397,771) and Lacy et al. (US 5,645,856).

The teachings of Ko, Whittle and Bechgaard are stated above.

Ko, Whittle and Bechgaard do not expressly teach colloidal silicon dioxide as a viscosity regulating agent.

Lacy teaches ingredients such as thickeners/suspending agents including colloidal silicon dioxide that can be incorporated in oil-based drug delivery systems (Col. 13, lines 58-67).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make an emulsion formulation of testosterone, as taught by Ko, test the serum level of testosterone and modify the formulation in order to achieve a serum level of greater than baseline for at least six hours after a single application during the process of routine experimentation, combine it with the self-emulsifying formulation comprising a lipophilic medicament, as taught by Whittle, and with the anhydrous composition for nasal delivery comprising oils and testosterone, as taught by Bechgaard, further use colloidal silicon dioxide as a thickener/suspending agent, as taught by Lacy, and produce the instant invention.

One of ordinary skill in the art would find it obvious to try various thickeners/suspending agents in emulsion formulations and would choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success. Please see MPEP 2141.

Regarding instant claim 37, the colloidal silicon dioxide would have been obvious over the colloidal silicon dioxide used as a thickener/suspending agent by Lacy (Col. 13, lines 58-67).

12. Claims 25-27, 31 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gizurarson et al. (US 2004/0005275 A1).

Gizurarson teaches pharmaceutical compositions especially suitable for mucosal administration as intranasal administration (Abstract) and comprise a PEG-fatty acid-mono-or diglyceride, an active substance and a physiologically acceptable vehicle (Page 1, [0005] - [0010]). The composition further comprises surfactants, HLB-controlling agents and viscosity controlling agents (Page 3, [0037]). Examples of biologically active substances and drugs include sex hormones such as testosterone (Page 3, [0043]). Polyoxyethylene sorbitan monooleate and lecithin are disclosed (Page 4, [0050]). Humectants such as glycerin, sorbitol and other excipients such as edible castor oil are disclosed (Page 5, [0052]).

Gizurarson does not expressly teach that the at least one sexual hormone drug is maintained at a serum level greater than baseline for at least six hours after a single application of the formulation.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a composition for nasal administration comprising testosterone, castor oil and surfactant, as suggested by Gizurarson, test the serum level of testosterone and modify the formulation in order to achieve a serum level of greater

than baseline for at least six hours after a single application during the process of routine experimentation.

One of ordinary skill in the art would do this because the components of the claimed composition are known in the art and testing the serum level of the active ingredient over time and modification of the composition to achieve desired serum levels is part of routine optimization unless there is evidence of criticality or unexpected results.

Therefore, claims 25-27, 31 and 42 are rendered obvious by Gizurarson.

13. Claims 25-26 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heckenmüller et al. (US 5,514,673).

Heckenmüller teaches a pharmaceutical composition comprising a lipophilic drug such as sex hormones (Col. 1, lines 6-11). The drug is dissolved in an oil such as a natural oil (Col. 2, lines 46-54). Natural oil may be used at a concentration of between 5 and 50% by weight related to the whole composition (Col. 3, lines 26-30). Lecithin is used in a concentration from 0.5 to 10% by weight (Col. 3, lines 31-32). Emulsifiers such as Tween 80 (polyoxyethylene sorbitan monooleate) is disclosed at a concentration of about 2% by weight that is suitable for nasal administration (Col. 3, lines 38-44). Components such as glycerol and sorbitol are also disclosed (Col. 3, lines 45-53).

Heckenmüller does not expressly teach that the at least one sexual hormone drug is maintained at a serum level greater than baseline for at least six hours after a single application of the formulation.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a composition for nasal administration comprising a sex hormone, natural oil and emulsifier, as suggested by Heckenmüller, test the serum level of testosterone and modify the formulation in order to achieve a serum level of greater than baseline for at least six hours after a single application during the process of routine experimentation.

One of ordinary skill in the art would do this because the components of the claimed composition are known in the art and testing the serum level of the active ingredient over time and modification of the composition to achieve desired serum levels is part of routine optimization unless there is evidence of criticality or unexpected results.

Therefore, claims 25-26 and 31 are rendered obvious by Heckenmüller.

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 25-42 and 44 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 6-8, 10-12, 16, 18-21 and 24-25 of copending Application No. 11/560,187 ('187 hereinafter). Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims and claims of '187 are drawn to a formulation for nasal application comprising at least one hormone drug, at least one lipophilic or partly lipophilic carrier and at least one compound having surface tension decreasing activity, an amount effective for *in situ* generation of an emulsion upon contact of the formulation with water. The difference is that component (b) of instant claim 1 recites the range of the lipophilic carrier as between 60% and 98% by weight of the formulation. It would be obvious to one of ordinary skill in the art to modify the percentage of the lipophilic carrier in the formulation for nasal application during the process of routine optimization. The recited percentage range would have been an obvious variant unless there is evidence of criticality or unexpected results.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

16. In light of the cancellation of claims 1-8, 10-13 and 20-24, the rejections with respect to these claims are rendered moot. However, newly added claims 25-42 and 44 are rejected on the ground of obviousness-type double patenting rejection (see above).

17. Applicant notes (see Page 7, filed 03/29/10) that a Terminal Disclaimer was filed on October 14, 2008.

18. However, the Terminal Disclaimer filed on October 14, 2008 was not approved since the attorney was not of record. Until such time that a Terminal Disclaimer is filed (with an attorney of record), the obviousness-type double patenting rejection will be maintained.

Conclusion

19. No claims are allowed.

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aradhana Sasan whose telephone number is (571) 272-9022. The examiner can normally be reached Monday to Thursday from 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax, can be reached at 571-272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Aradhana Sasan/
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